A. Rejection under §102(b)

The Examiner states that the §102(b) rejection would be reconsidered upon determination of the contents of the provisional application and asks for Applicants help in this regard. Accordingly, Applicants submit herewith a copy of the provisional application serial no. 60/028,269.

The Examiner is directed to the disclosure on page 20, line 12 to page 22, line 16 where targeting ligands attached to a lipid-polymer moiety are described. Page 25, line 13 to page 27, line 19 gives specific synthetic reaction schemes for attaching a targeting ligand to the distal end of a polymer chain attached to a lipid. Finally, on page 29, lines 29-34 preparation of targeted-liposomes using the targeting conjugates is described.

Thus, the present claims are entitled to the priority date of October 11, 1996. Torchilin *et al.* was granted July 9, 1996, less than a year before applicants priority. This document, therefore, does not qualify as prior art under 35 U.S.C. §102(b).

B. Rejection under 35 U.S.C. §102(a)

Claims 21-25, 60, and 71 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Torchilin *et al.* This rejection is respectfully traversed.

Summaries of the instant claims and of the Torchilin *et al.* document are provided in Applicants' response submitted January 3, 2002.

1. Analysis of the Rejection

The Examiner asserts that the pending claims when interpreted in their broadest sense are anticipated by Torchilin *et al.* in its disclosure of a chelating moiety attached to a lipid-polymer. The Examiner asserts that the chelating moiety is a "targeting" moiety because, in the absence of antibody-mediated targeting, the liposomes accumulate in liver, spleen, lymph nodes, and bone marrow (e.g., the organs of the reticuloendothelial system (RES)).

This argument relies on the assumptions that:

1. a chelating moiety is a "targeting" ligand; and that
2. the chelating moiety acts to "target" the liposomes to a desired organ.

These assumptions are incorrect for the reasons given below.

With respect to the first assumption, it is clear from the disclosure of Torchilin *et al.* that a chelating moiety is not a targeting moiety. The chelating agent in Torchilin *et al.* is in fact a radiocontrast agent – i.e., a metal-chelator complex, such as gadolinium diethylenetriamine pentaacetic acid. Torchilin *et al.* make imminently clear that a metal-chelator agent is not a targeting agent by the disclosure on Col. 8, lines 63-66, where after administration of liposomes containing the metal-chelating agent, the

> "accumulation sites were those expected for conventional liposomes: liver, spleen, lymph nodes, and bone marrow".

Torchilin *et al.* go on to state that other organs can be imaged using antibody-mediated targeting of the liposomes. Clearly, from this, Torchilin *et al.* teach that liposomes with metal-chelating agents act like conventional liposomes – *e.g.,* liposomes lacking a targeting moiety.

This is further supported by the disclosure on Col. 9, lines 7-22, where Torchilin *et al.* teach that

> "liposomes can be further modified to alter their natural targeting of liposomes for the macrophage-monocyte system, *e.g.*, liver, spleen, bone marrow, and lymph nodes."

And,

> "to obtain a liposome or micelle that is targeted for a specific antigen tissue, organ, or in the body, a targeting group is bound to the lipid membrane surface of the liposome...". (Col. 9, lines 19-22).

In summary, Torchilin *et al.* clearly teach that (1) liposomes with surface-attached metal-chelating agents accumulate *in vivo* as expected for "conventional" liposomes (Col. 8, lines 64-66) and (2) to alter this, a targeting moiety such as an antibody can be attached to the liposome surface. That is, liposomes with a chelating agent do nothing to alter the natural tendency of liposomes to accumulate in the organs of the RES. The presence or absence of a chelating agent does nothing to alter this. Thus, Applicant is completely and utterly baffled by the Examiner's belief that a metal-chelator, radiocontrast agent can act to "direct" or "target" a liposome to a particular *in vivo* site,

when clearly the metal-chelator does nothing to change the natural liposomal distribution to the RES organs.

The Examiner's argument relies on the second assumption noted above that the chelating moiety acts to "target" the liposomes to a desired organ. From the discussion above, it is clear that this is not the case. The chelating moiety does not cause the liposomes to go toward a particular organ, *since liposomes with the chelating moiety accumulate identically as do liposomes without the chelating agent.* (Col. 8, lines 64-66).

According to the M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". Since Torchilin *et al.* fail to teach a lipid-polymer-targeting ligand conjugate the standard for anticipation has not been met. Withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

II. Rejection under 35 U.S.C. §103

Claims 21-32 and 57-81 were rejected under 35 U.S.C. §103 as allegedly obvious over Torchilin *et al.* further in view of Harris *et al.* (U.S. Patent No. 5,932,462). This rejection is respectfully traversed for the following reasons.

Summaries of the present invention and the cited art are provided in Applicants' response submitted January 3, 2002.

A. Anaysis

The Examiner asserts that it would have been obvious to use any targeting molecule in the polymer complex of Torchilin *et al.* with the expectation of obtaining at least similar results since Harris *et al.* teach that any ligand can be coupled to the hydrophilic polymer system.

In making this assertion, the Examiner continues to rely on the assumption that a metal-chelating agent acts as a targeting moiety in a liposome, and that it would be obvious to substitute any of the targeting ligands of Harris *et al.* for the polychelating agent.

The assumption that the metal-chelating agent is a targeting moiety has been discussed extensively above. Since the presence of the metal-chelating agent does not alter the *in vivo* distribution from that of liposomes with no chelating agent, there is simply no way that an assertion that the metal-chelating agent is a targeting moiety can stand. For all the reasons given above, it is evident that the metal-chelating agent is not a targeting moiety.

The Examiner proposes another rational for using the teachings of Torchilin *et al.* and Harris *et al.* to arrive at the present claims of a lipid-polymer-targeting ligand conjugate, with the targeting ligand attached to the distal end of the polymer. The Examiner proposes to recognize the teaching in Harris *et al.* that PEG can be bifunctional and that one functional group could be attached to the liposome surface in accord with Torchilin *et al.* and the other functional group to the targeting chelating ligand. (Office action dated April 24, 2002, page 5, lines 1-9).

Again, the rational relies on the polychelating agent being a targeting moiety, and must fail for that reason.

Another possibility that the Examiner seems to suggest to arrive at the present claims is to omit the chelating agent of Torchilin *et al.* and to substitute a targeting moiety as taught by Harris *et al.* (Office action dated April 24, 2002, page 4, lines 1-2; "Torchilin does not specifically teach that these ligands [other targeting groups such as enzymes, lectins, and antibodies] could be attached to the polymer instead of the polychelating agents. (brackets and emphasis added); Office action page 5, lines 12-14 stating it is "obvious to couple a targeting ligand and the liposomal surface to PEG with a reasonable expectation of success.")

Surely the Examiner cannot intend for the chelating agent to be omitted from Torchilin *et al.*, since such a modification would render the liposomes unsuitable for their intended use as radiocontrast agents. (see MPEP §2143.01 that proposed modification cannot render the prior art unsatisfactory for its intended purpose).

In the final analysis, the combination of Torchilin *et al.* and Harris *et al.* fail to teach a lipid-polymer-targeting agent. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

It is respectfully submitted that each of the pending claims 21-32 and 57-81 are in condition for allowance. A Notice of Allowance is respectfully requested.

The Examiner is invited to contact Applicants' representative at (650) 838-4402 as needed.

Respectfully submitted,

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Date: 4/8/03

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